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Intramolecular CuCl-Mediated Oxidative Coupling of Alkenyltrimethylstannane Functions: An Effective Method for the Construction of Carbocyclic 1,3-Diene Systems

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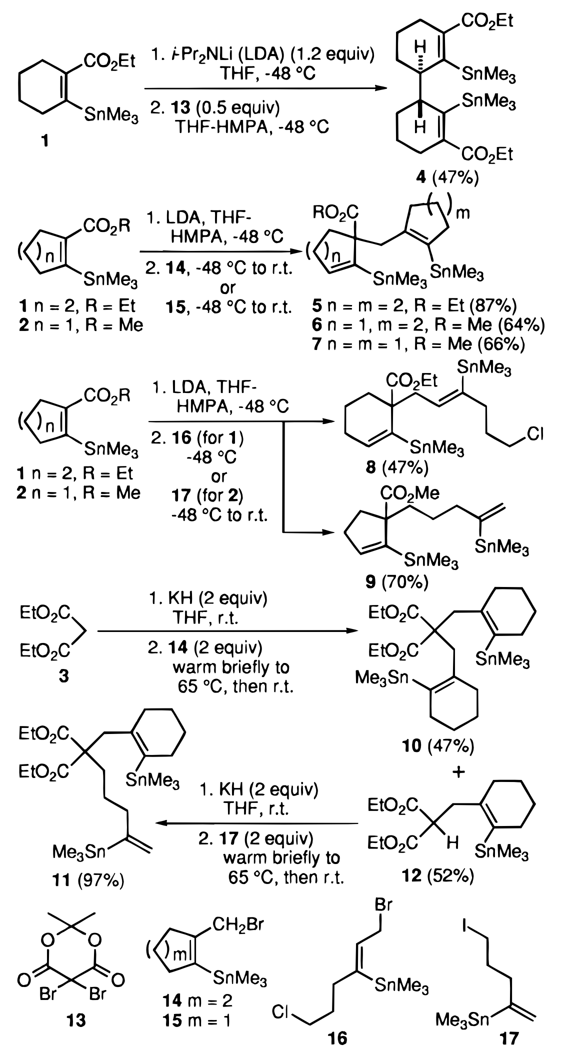
The discovery of new, efficient methods for the construction of carbon−carbon bonds represents an ongoing, central theme of research in the area of organic synthesis. In this context, the palladium(0)-catalyzed intermolecular[1,2] and intramolecular[3] cross couplings of alkenyltrialkylstannane functions with alkenyl triflates, iodides, or bromides constitute valuable processes for the stereospecific preparation of acyclic and carbocyclic conjugated diene systems. A recent report[4] from this laboratory disclosed that intramolecular coupling of alkenyltrimethylstannane moieties with alkenyl halide (Br, I) functions can also be performed efficiently by treatment of the requisite substrates with CuCl ($\sim$2−3 equiv) in *N,N*-dimethylformamide (DMF). We report herein the novel finding that CuCl also mediates the highly efficient intramolecular coupling of two alkenyltrimethylstannane functions. As outlined below, this method has thus far successfully effected the closure of 4-, 5-, 6-, 7-, and 8-membered rings.

The substrates **4**−**11** employed in this study were prepared as summarized in Scheme 1. Treatment of the lithium enolate of the β-trimethylstannyl α,β-unsaturated ester **1**[5,6] with 0.5 equiv of dibromo Meldrum's acid (**13**)[8] provided the "dimeric" substance **4**.[9,10] Alkylation of **1** with the allylic bromide **14**[11,12] provided the bis(alkenylstannane) **5**, while similar reactions involving **2**[7] and the bromides **14**[11,12] and **15**[11,12] produced the structurally related compounds **6** and **7**. On the other hand, alkylation of **1** and **2** with the allylic bromide **16**[12,13] and the primary iodide **17**,[3a,12] respectively, gave the corresponding functionalized substances **8** and **9**.

Scheme 1



The substrates **10** and **11** were also prepared via alkylation chemistry (Scheme 1). Thus, reaction of the potassium enolate of diethyl malonate with the bromide **14**[11,12] gave a mixture of the di- and monoalkylation products **10** and **12**, respectively. Transformation of **12** into the bis(alkenylstannane) **11** was achieved via a straightforward alkylation involving use of the iodide **17**[3a,12] as the electrophile.

Rapid addition of a solution of **4** (1 equiv) in *N,N*-dimethylformamide (DMF, $\sim$4 mL per millimole of **4**) to a warm ($\sim$60 °C), stirred slurry of CuCl ($\sim$5 equiv) in DMF ($\sim$4 mL per millimole of CuCl), followed by stirring of the mixture for 15 min, produced the structurally novel tricycle **18** in 67% yield (Scheme 2). Since, at this stage, the relative configurations of **4** and **18** were not known, the crystalline product (mp 124−125 °C, from Et$_2$O−pentane) was subjected to an X-ray crystallographic study.[14] It was thus established conclusively that this material possesses the structure shown in formula **18**. Interestingly, in the solid state, the conjugated diene system of **18** is notably twisted away from planarity; the torsion angle traced in going from C-3 to C-12 (via C-2 and C-1) is 66°.

The closures of 5-membered rings via the new coupling method, using protocols very similar to those employed for **4**, are illustrated by the conversions of **5**−**8** into **19**−**22**, respectively. Each of these reactions is clean and efficient, and thus, by use of experimentally undemanding chemistry, the syntheses of functionalized tricyclo[7.4.0.0^{2,7}]tridecane (**19**), tricyclo-

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[1] (a) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508. (b) Mitchell, T. N. *Synthesis* **1992**, 803.

[2] Scott, W. J.; Crisp, G. T.; Stille, J. K. *Org. Synth.* **1990**, *68*, 116.

[3] (a) Piers, E.; Friesen, R. W.; Keay, B. A. *Tetrahedron* **1991**, *47*, 4555. (b) Piers, E.; Friesen, R. W. *Can. J. Chem.* **1992**, *70*, 1204. (c) Piers, E.; Friesen, R. W.; Rettig, S. J. *Can. J. Chem.* **1992**, *70*, 1385.

[4] Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609.

[5] All new compounds reported herein exhibit spectra in accord with assigned structures and gave satisfactory elemental (C, H) analyses and/or molecular mass determinations (high-resolution mass spectrometry).

[6] Compound **1** was prepared from 2-ethoxycarbonylcyclohexanone via a method similar to that described previously for the corresponding methyl ester.[7]

[7] Piers, E.; Tse, H. L. A. *Can. J. Chem.* **1993**, *71*, 983.

[8] Bloch, R. *Synthesis* **1978**, 140.

[9] The yield of this process, as well as that of each of the other alkylations described herein, has not yet been optimized.

[10] Presumably, the enolate of **1** reacts with **13** to afford (primarily) the 3-bromo derivative of **1**, which then alkylates the γ-position of the enolate to produce **4**. This interesting transformation is currently being studied in more detail. The relative configuration of **4** was determined by an X-ray crystallographic study on the corresponding cyclization product **18** (vide infra).

[11] Reduction (i-Bu$_2$AlH, THF) of the esters **1** and **2**, followed by treatment of the acquired alcohols with Ph$_3$PBr$_2$ in CH$_2$Cl$_2$ in the presence of imidazole, provided the required allylic bromides **14** (86%) and **15** (92%), respectively.

[12] Solutions (THF) of each of the alkylating agents employed in this work were passed through a plug of dry basic alumina immediately prior to use.

[13] The bromide **16** was derived (Ph$_3$PBr$_2$ in CH$_2$Cl$_2$ in the presence of imidazole, 85%) from the corresponding allylic alcohol.[3c]

[14] Details of this X-ray crystallographic study will be presented elsewhere. We are very grateful to Dr. Steven J. Rettig for carrying out this structure determination.

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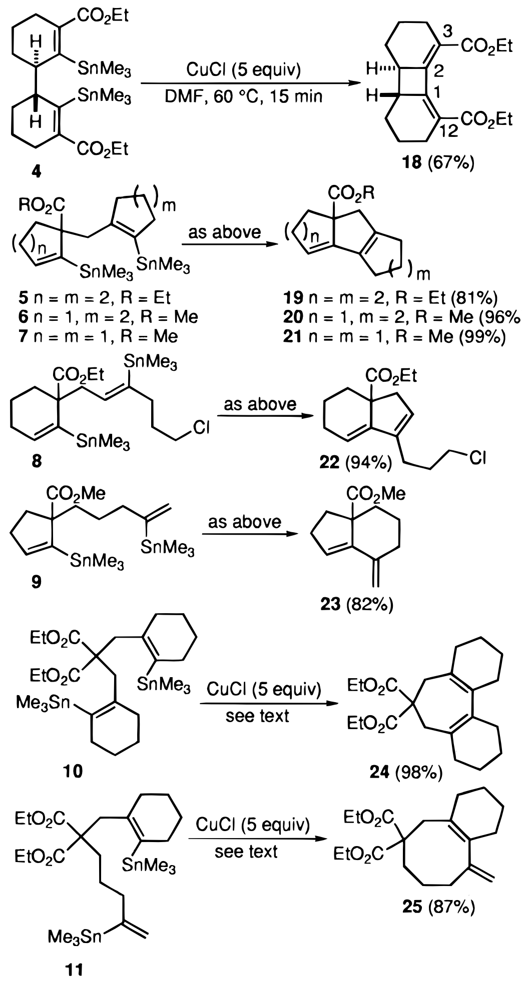
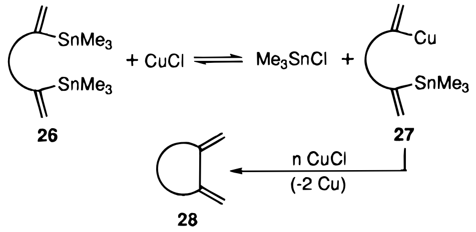
Scheme 2



Scheme 3



$[7.3.0.0^{2,7}]$dodecane (**20**), tricyclo$[6.3.0.0^{2,6}]$undecane (**21**), and bicyclo[4.3.0]nonane (**22**) ring systems are readily accomplished.

To demonstrate further the versatility and effectiveness of the method, the possibility of forming 6-, 7-, and 8-membered rings was investigated. These processes are exemplified by the conversions of **9**−**11** into the corresponding dienes **23**,[3a] **24**, and **25**. It should be noted that, for each of the transformations **10** → **24** and **11** → **25**, somewhat more dilute reaction mixtures (0.017 mmol of CuCl per milliliter of DMF) were employed. Furthermore, in each of these reactions, the solution of the substrate in DMF was added slowly (over a period of ∼15 min) to the mixture of CuCl and DMF, and, after the addition was complete, stirring was continued for an additional 15 min. Under these conditions, both reactions were highly efficient.

The results summarized above show clearly that the CuCl-mediated intramolecular coupling of alkenyltrimethylstannane functions constitutes an effective, potentially valuable method for the synthesis of carbocyclic systems containing conjugated diene units. Collectively, the products **18**−**25** display an impressive array of carbon skeletons and, in addition, exhibit a diverse set of functionality. The efficient syntheses of the novel substances containing 4-, 7-, and 8-membered rings (**18**, **24**, and **25**, respectively) are particularly noteworthy. Obviously, many extensions to this work can be envisaged, including the prospect of using the methodology for the construction of larger ring systems and for the syntheses of structurally novel natural and non-natural products. We are actively pursuing a number of possibilities.

At present, the mechanistic pathway followed by the new cyclization method remains obscure. However, it has been found that complete conversion of starting material to product within a relatively short reaction time (e.g., 15 min) requires at least 4 equiv of CuCl. We have routinely employed ∼5 equiv of the Cu(I) salt. Furthermore, it was determined that, for each millimole of substrate converted to product, 2 mmol of copper metal is produced.[15] Also, the presence of water in the reaction mixture does not appear to have a deleterious effect on the efficiency of the reaction. For example, treatment of substrate **6** with CuCl (5 equiv) in DMF (60 °C) containing 1 equiv of water provided product **20** in 91% yield. Based on previous studies,[16,17] it is reasonable to propose that the cyclization process is initiated by transmetalation of one of the Me_3Sn groups in the substrate (Scheme 3, general formula **26**), to afford Me_3SnCl and the intermediate represented by the general formula **27**. A proposal regarding the mechanistic details of the transformation of **27** into the product **28** with the accompanying formation of 2 equiv of copper metal will have to await further experimentation.

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Supporting Information Available: Typical experimental procedures describing the preparation of **15** from **2**, the use of **2** and **15** to prepare **7**, and the CuCl-mediated ring closure of **7** to **21** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(15) The effect of using varying amounts of CuCl on conversion of starting material into product, and the quantification of the amount of copper metal produced during the cyclization process, were determined by studying the transformation of **6** into **20**. Details of these investigations will be given in a full account of this work.

(16) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(17) Piers, E.; McEachern, E. J.; Burns, P. A. *J. Org. Chem.* **1995**, *60*, 2322.